

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of

TAKENOUCHI, KAZUYA, et al.

Divisional of Appln. No.: 09/830,167
Filed April 23, 2001

Group Art Unit: Not Yet Assigned

Confirmation No.: Not Yet Assigned

Examiner: Not Yet Assigned

Filed: January 4, 2002

For: VITAMIN D3 DERIVATIVE AND TREATING AGENT FOR INFLAMMATORY
RESPIRATORY DISEASE USING SAME

PRELIMINARY AMENDMENT

Commissioner for Patents
Washington, D.C. 20231

Sir:

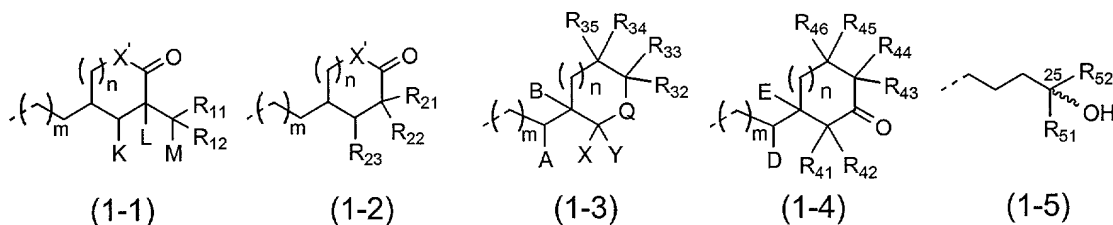
Prior to examination, please amend the above-identified application as follows:

IN THE SPECIFICATION:

Amend the specification by inserting before the first line the sentence:

This is a Divisional of Application No. 09/830,167 filed April 23, 2001, the disclosure of
which is incorporated herein by reference.

**Page 6, please delete the paragraph at lines 18-19 with formulas (1-1) to (1-5), and
replace it with the following new paragraph:**

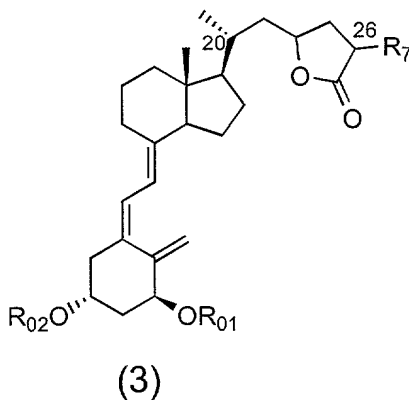


IN THE CLAIMS:

Please cancel claims 1-44

Please enter new claims 45-54:

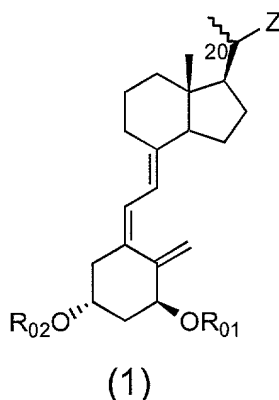
45. A method for treating an inflammatory respiratory disease comprising administering to a subject a therapeutically effective amount of a vitamin D₃ derivative described by the following general formula (3) or pharmaceutically permissible solvate thereof,



wherein, R₀₁ and R₀₂ are each independently a hydrogen atom, a trimethylsilyl group, a triethylsilyl group, a t-butyltrimethylsilyl group, an acetyl group, a methoxymethyl group or a tetrahydro-4H-pyran-2-yl group; the configuration of the carbon atom at the 20-position is (R)-

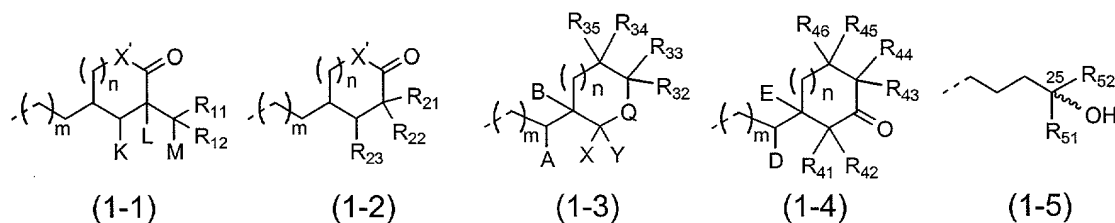
configuration; R_7 is a methyl group or a methylene group; when R_7 is a methylene group, the bond between R_7 and the carbon atom at the 26-position is double bond.

46. A method for treating an inflammatory respiratory disease comprising administering to a subject a therapeutically effective amount of a vitamin D₃ derivative expressed by the following general formula (1) or pharmaceutically permissible solvates thereof,



{wherein, R_{01} and R_{02} are each independently a hydrogen atom, a trimethylsilyl group, a triethylsilyl group, a t-butyldimethylsilyl group, an acetyl group, a methoxymethyl group or a tetrahydro-4H-pyran-2-yl group;

Z is one out of the following formulae (1-1), (1-2), (1-3), (1-4) or (1-5),



[in the above formulae (1-1) to (1-5),

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m is an integer of 0 to 2;

n is an integer of 0 to 2;

X' is an oxygen atom or NH;

R₁₁ and R₁₂ are identical to or different from each other, and express a hydrogen atom or a C₁-C₄ alkyl group;

K, L and M are each a hydrogen atom; M is a hydrogen atom, and K and L together express a single bond and express a double bond in cooperation with the single bond already shown in the formula; or K is a hydrogen atom, and L and M together express a single bond and express a double bond in cooperation with the single bond already shown in the formula;

R₂₁, R₂₂ and R₂₃ are identical to or different from each other, and they are a hydrogen atom, a hydroxy group, a carboxyl group, a trifluoromethyl group, a pentafluoroethyl group, a C₁-C₄ alkyloxycarbonyl group, a C₂-C₅ acyloxy group, a C₁-C₄ alkyloxy group or a C₁-C₄ alkyl group which may be substituted with a hydroxyl group, a C₂-C₅ acyloxy group or a C₁-C₄ alkyloxy group, or R₂₁ and R₂₂ together may express a C₃-C₆ cyclic alkyl group in cooperation with the carbon atom to which they are bonded;

Q expresses >C(-F)-R₃₁ or >N-R₃₁, and herein R₃₁ is a hydrogen atom, a hydroxyl group, a trifluoromethyl group, a pentafluoroethyl group, a C₂-C₅ acyloxy group, a C₁-C₄ alkyloxy group or a C₁-C₄ alkyl group which may be substituted with a hydroxy group, a C₂-C₅ acyloxy group or a C₁-C₄ alkyloxy group;

R₃₂, R₃₃, R₃₄ and R₃₅ are identical to or different from each other, and they are a hydrogen atom, a hydroxyl group, a C₁-C₄ alkyl group or a C₂-C₅ acyloxy group;

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A and B are identical to or different from each other, and they express a hydrogen atom or a hydroxyl group, or together express a single bond and form a double bond in cooperation with the single bond already shown in the formula;

X and Y together express a carbonyl group in cooperation with the carbon atom to which they are bonded, one of them is a hydrogen atom and the other is a hydroxyl group, or one of them is a hydrogen atom and the other is a C₂-C₅ acyloxy group;

R₄₁ and R₄₂ are identical to or different from each other, and they express a hydrogen atom, a hydroxyl group, a trifluoromethyl group, a pentafluoroethyl group, a C₂-C₅ acyloxy group, a C₁-C₄ alkyloxy group or a C₁-C₄ alkyl group which may be substituted with a hydroxyl group, a C₂-C₅ acyloxy group or a C₁-C₄ alkyloxy group, or both the members together express a C₁-C₅ alkylidene group, or they express a C₃-C₆ cyclic alkyl group in cooperation with the carbon atom to which they are bonded;

R₄₃ and R₄₄ are identical to or different from each other, and they express a hydrogen atom, a hydroxyl group, a trifluoromethyl group, a pentafluoroethyl group, a C₂-C₅ acyloxy group, a C₁-C₄ alkyloxy group or a C₁-C₄ alkyl group which may be substituted with a hydroxyl group, a C₂-C₅ acyloxy group or a C₁-C₄ alkyloxy group, or both the members together express a C₁-C₅ alkylidene group, or express a C₃-C₆ cyclic alkyl group in cooperation with the carbon atom to which they are bonded;

R₄₅ and R₄₆ are identical to or different from each other, and they express a hydrogen atom, a hydroxyl group, a trifluoromethyl group, a pentafluoroethyl group, a C₂-C₅ acyloxy group, a C₁-C₄ alkyloxy group or a C₁-C₄ alkyl group which may be substituted with a hydroxyl group, a C₂-C₅ acyloxy group or a C₁-C₄ alkyloxy group;

D and E express each a hydrogen atom, D is a hydroxy group and E expresses a hydrogen atom, D and E together express a single bond and express a double bond in cooperation with the single bond already shown in the formula, or E and R₄₁ together express a single bond and express a double bond in cooperation with the single bond already shown in the formula, wherein D expresses a hydrogen atom or a hydroxy group; and R₄₂ expresses a hydrogen atom, a hydroxyl group, a trifluoromethyl group, a pentafluoroethyl group, a C₂-C₅ acyloxy group, a C₁-C₄ alkyloxy group or a C₁-C₄ alkyl group which may be substituted with a hydroxyl group, a C₂-C₅ acyloxy group or a C₁-C₄ alkyloxy group;

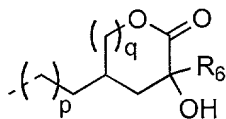
R₅₁ expresses -CONR₅₁₁R₅₁₂, -COR₅₁₃ or -C(OH) R₅₁₄R₅₁₅, wherein R₅₁₁ and R₅₁₂ are identical to or different from each other, and they are a hydrogen atom or a C₁-C₄ alkyl group, or both the members together express a nitrogen-containing C₃-C₈ alkyl ring or a morpholino group in cooperation with the nitrogen atom to which they are bonded; and R₅₁₃, R₅₁₄ and R₅₁₅ are identical to or different from each other, and they express a C₁-C₄ alkyl group;

R₅₂ expresses a methyl group, an ethyl group, a trifluoromethyl group or a pentafluoroethyl group,]

with the proviso that the following compounds (a), (b) and (c) are excluded,

(a) a compound in which the groups of one combination out of R₂₁ and R₂₂, R₃₂ and R₃₃, R₃₄ and R₃₅, R₄₁ and R₄₂, R₄₃ and R₄₄, and R₄₅ and R₄₆ are both hydroxy groups, both alkyloxy groups, or a hydroxy group and an alkyloxy group,

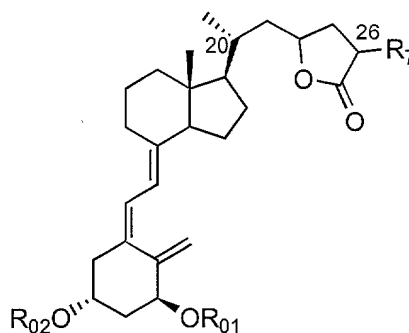
(b) a compound expressed by the above formula (1) in which Z is the following formula (1-6),



(1-6)

(wherein, p and q are each 0 or the integer 1; R₆ is a hydrogen atom or a C₁-C₄ alkyl group), and

(c) a compound of the following formula (2),



(2)

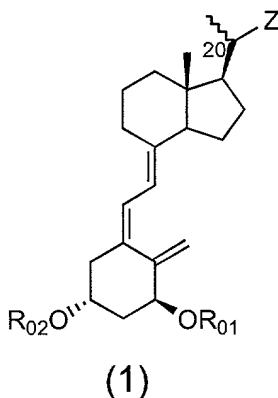
(wherein, R₀₁ and R₀₂ are defined in the same manner as in the above formula (1); the configuration of the carbon atom at the 20-position is (R)-configuration; R₇ is a methyl group or a methylene group; when R₇ is a methylene group, the bond between R₇ and the carbon atom at the 26-position is double bond)).

47. A treating agent for an inflammatory respiratory disease described in Claim 45 or 46, wherein the inflammatory respiratory disease is one or not less than two kinds of inflammatory respiratory diseases selected from a group consisting of acute upper airway infection, chronic sinusitis, allergic rhinitis, chronic lower airway infection, pulmonary emphysema, pneumonia, bronchial asthma, tuberculosis sequela, acute respiratory distress syndrome, cystic fibrosis and pulmonary fibrosis.

48. A treating agent for an inflammatory respiratory disease described in Claim 47, wherein the acute upper airway infection is one or not less than two kinds of diseases selected from a group consisting of common cold, acute pharyngitis, acute rhinitis, acute sinusitis, acute tonsillitis, acute pharyngitis, acute epiglottitis and acute bronchitis.

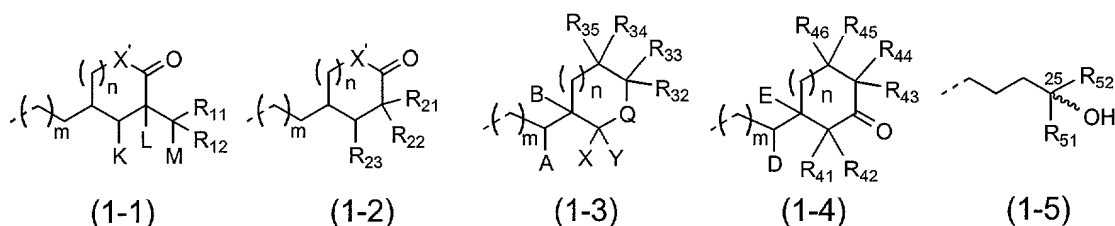
49. A treating agent for an inflammatory respiratory disease described in Claim 47, wherein the chronic lower airway infection is one or not less than two kinds of diseases selected from a group consisting of chronic bronchitis, diffuse panbronchiolitis and bronchiectasis.

50. A method for treating one or not less than two kinds of inflammatory respiratory diseases selected from a group consisting of chronic bronchitis, diffuse panbronchiolitis, bronchiectasis, bronchial asthma, pulmonary emphysema, tuberculosis sequela and cystic fibrosis comprising administering to a subject a therapeutically effective amount of a vitamin D₃ derivative expressed by the following formula (1) or pharmaceutically permissible solvate thereof:



{wherein, R_{01} and R_{02} are each independently a hydrogen atom, a trimethylsilyl group, a triethylsilyl group, a t-butyldimethylsilyl group, an acetyl group, a methoxymethyl group or a tetrahydro-4H-pyran-2-yl group;

Z is one out of the following formulae (1-1), (1-2), (1-3), (1-4) or (1-5),



[in the above formulae (1-1) to (1-5),

m is an integer of 0 to 2;

n is an integer of 0 to 2;

X' is an oxygen atom or NH;

R_{11} and R_{12} are identical to or different from each other, and express a hydrogen atom or a C_1 - C_4 alkyl group;

K, L and M are each a hydrogen atom; M is a hydrogen atom, and K and L together express a single bond and express a double bond in cooperation with the single bond already shown in the formula; or K is a hydrogen atom, and L and M together express a single bond and express a double bond in cooperation with the single bond already shown in the formula;

R_{21} , R_{22} and R_{23} are identical to or different from each other, and they are a hydrogen atom, a hydroxy group, a carboxyl group, a trifluoromethyl group, a pentafluoroethyl group, a C_1 - C_4 alkyloxycarbonyl group, a C_2 - C_5 acyloxy group, a C_1 - C_4 alkyloxy group or a C_1 - C_4 alkyl

group which may be substituted with a hydroxyl group, a C₂-C₅ acyloxy group or a C₁-C₄ alkyloxy group, or R₂₁ and R₂₂ together may express a C₃-C₆ cyclic alkyl group in cooperation with the carbon atom to which they are bonded;

Q expresses >C(-F)-R₃₁ or >N-R₃₁, and herein R₃₁ is a hydrogen atom, a hydroxyl group, a trifluoromethyl group, a pentafluoroethyl group, a C₂-C₅ acyloxy group, a C₁-C₄ alkyloxy group or a C₁-C₄ alkyl group which may be substituted with a hydroxy group, a C₂-C₅ acyloxy group or a C₁-C₄ alkyloxy group;

R₃₂, R₃₃, R₃₄ and R₃₅ are identical to or different from each other, and they are a hydrogen atom, a hydroxyl group, a C₁-C₄ alkyl group or a C₂-C₅ acyloxy group;

A and B are identical to or different from each other, and they express a hydrogen atom or a hydroxyl group, or together express a single bond and form a double bond in cooperation with the single bond already shown in the formula;

X and Y together express a carbonyl group in cooperation with the carbon atom to which they are bonded, one of them is a hydrogen atom and the other is a hydroxyl group, or one of them is a hydrogen atom and the other is a C₂-C₅ acyloxy group;

R₄₁ and R₄₂ are identical to or different from each other, and they express a hydrogen atom, a hydroxyl group, a trifluoromethyl group, a pentafluoroethyl group, a C₂-C₅ acyloxy group, a C₁-C₄ alkyloxy group or a C₁-C₄ alkyl group which may be substituted with a hydroxyl group, a C₂-C₅ acyloxy group or a C₁-C₄ alkyloxy group, or both the members together express a C₁-C₅ alkylidene group, or they express a C₃-C₆ cyclic alkyl group in cooperation with the carbon atom to which they are bonded;

R₄₃ and R₄₄ are identical to or different from each other, and they express a hydrogen atom, a hydroxyl group, a trifluoromethyl group, a pentafluoroethyl group, a C₂-C₅ acyloxy group, a C₁-C₄ alkyloxy group or a C₁-C₄ alkyl group which may be substituted with a hydroxyl group, a C₂-C₅ acyloxy group or a C₁-C₄ alkyloxy group, or both the members together express a C₁-C₅ alkylidene group, or express a C₃-C₆ cyclic alkyl group in cooperation with the carbon atom to which they are bonded;

R₄₅ and R₄₆ are identical to or different from each other, and they express a hydrogen atom, a hydroxyl group, a trifluoromethyl group, a pentafluoroethyl group, a C₂-C₅ acyloxy group, a C₁-C₄ alkyloxy group or a C₁-C₄ alkyl group which may be substituted with a hydroxyl group, a C₂-C₅ acyloxy group or a C₁-C₄ alkyloxy group;

D and E express each a hydrogen atom, D is a hydroxy group and E expresses a hydrogen atom, D and E together express a single bond and express a double bond in cooperation with the single bond already shown in the formula, or E and R₄₁ together express a single bond and express a double bond in cooperation with the single bond already shown in the formula, wherein D expresses a hydrogen atom or a hydroxy group; and R₄₂ expresses a hydrogen atom, a hydroxyl group, a trifluoromethyl group, a pentafluoroethyl group, a C₂-C₅ acyloxy group, a C₁-C₄ alkyloxy group or a C₁-C₄ alkyl group which may be substituted with a hydroxyl group, a C₂-C₅ acyloxy group or a C₁-C₄ alkyloxy group;

R₅₁ expresses -CONR₅₁₁R₅₁₂, -COR₅₁₃ or -C(OH) R₅₁₄R₅₁₅, wherein R₅₁₁ and R₅₁₂ are identical to or different from each other, and they are a hydrogen atom or a C₁-C₄ alkyl group, or both the members together express a nitrogen-containing C₃-C₈ alkyl ring or a morpholino group

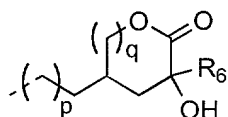
in cooperation with the nitrogen atom to which they are bonded; and R_{513} , R_{514} and R_{515} are identical to or different from each other, and they express a C_1 - C_4 alkyl group;

R_{52} expresses a methyl group, an ethyl group, a trifluoromethyl group or a pentafluoroethyl group,]

with the proviso that the following compounds (a), (b) and (c) are excluded,

(a) a compound in which the groups of one combination out of R_{21} and R_{22} , R_{32} and R_{33} , R_{34} and R_{35} , R_{41} and R_{42} , R_{43} and R_{44} , and R_{45} and R_{46} are both hydroxy groups, both alkyloxy groups, or a hydroxy group and an alkyloxy group,

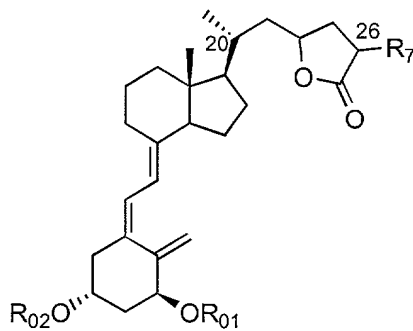
(b) a compound expressed by the above formula (1) in which Z is the following formula (1-6),



(1-6)

(wherein, p and q are each 0 or the integer 1; R_6 is a hydrogen atom or a C_1 - C_4 alkyl group), and

(c) a compound of the following formula (2),

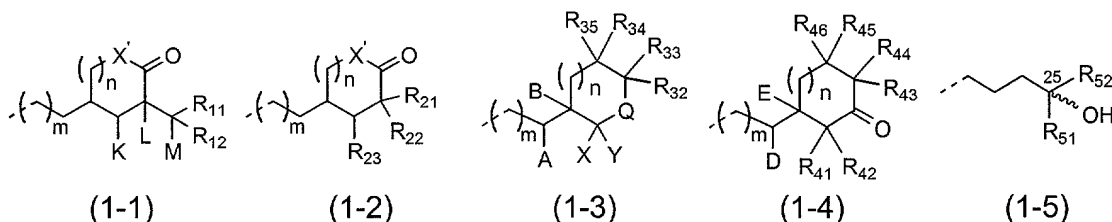


(2)

51. A method for treating a disease selected from a group consisting of malignant tumors, rheumatoid arthritis, osteoporosis, diabetes mellitus, hypertension, alopecia, acne, psoriasis and dermatitis comprising administering to a subject a therapeutically effective amount of a vitamin D₃ derivative expressed by the following formula (1) or pharmaceutically permissible solvate thereof:



Z is one out of the following formulae (1-1), (1-2), (1-3), (1-4) or (1-5),



[in the above formulae (1-1) to (1-5),

m is an integer of 0 to 2;

n is an integer of 0 to 2;

X' is an oxygen atom or NH;

R₁₁ and R₁₂ are identical to or different from each other, and express a hydrogen atom or a C₁-C₄ alkyl group;

K, L and M are each a hydrogen atom; M is a hydrogen atom, and K and L together express a single bond and express a double bond in cooperation with the single bond already shown in the formula; or K is a hydrogen atom, and L and M together express a single bond and express a double bond in cooperation with the single bond already shown in the formula;

R₂₁, R₂₂ and R₂₃ are identical to or different from each other, and they are a hydrogen atom, a hydroxy group, a carboxyl group, a trifluoromethyl group, a pentafluoroethyl group, a C₁-C₄ alkyloxycarbonyl group, a C₂-C₅ acyloxy group, a C₁-C₄ alkyloxy group or a C₁-C₄ alkyl group which may be substituted with a hydroxyl group, a C₂-C₅ acyloxy group or a C₁-C₄ alkyloxy group, or R₂₁ and R₂₂ together may express a C₃-C₆ cyclic alkyl group in cooperation with the carbon atom to which they are bonded;

Q expresses $>C(-F)-R_{31}$ or $>N-R_{31}$, and herein R_{31} is a hydrogen atom, a hydroxyl group, a trifluoromethyl group, a pentafluoroethyl group, a C_2-C_5 acyloxy group, a C_1-C_4 alkyloxy group or a C_1-C_4 alkyl group which may be substituted with a hydroxy group, a C_2-C_5 acyloxy group or a C_1-C_4 alkyloxy group;

R_{32} , R_{33} , R_{34} and R_{35} are identical to or different from each other, and they are a hydrogen atom, a hydroxyl group, a C_1-C_4 alkyl group or a C_2-C_5 acyloxy group;

A and B are identical to or different from each other, and they express a hydrogen atom or a hydroxyl group, or together express a single bond and form a double bond in cooperation with the single bond already shown in the formula;

X and Y together express a carbonyl group in cooperation with the carbon atom to which they are bonded, one of them is a hydrogen atom and the other is a hydroxyl group, or one of them is a hydrogen atom and the other is a C_2-C_5 acyloxy group;

R_{41} and R_{42} are identical to or different from each other, and they express a hydrogen atom, a hydroxyl group, a trifluoromethyl group, a pentafluoroethyl group, a C_2-C_5 acyloxy group, a C_1-C_4 alkyloxy group or a C_1-C_4 alkyl group which may be substituted with a hydroxyl group, a C_2-C_5 acyloxy group or a C_1-C_4 alkyloxy group, or both the members together express a C_1-C_5 alkylidene group, or they express a C_3-C_6 cyclic alkyl group in cooperation with the carbon atom to which they are bonded;

R_{43} and R_{44} are identical to or different from each other, and they express a hydrogen atom, a hydroxyl group, a trifluoromethyl group, a pentafluoroethyl group, a C_2-C_5 acyloxy group, a C_1-C_4 alkyloxy group or a C_1-C_4 alkyl group which may be substituted with a hydroxyl group, a C_2-C_5 acyloxy group or a C_1-C_4 alkyloxy group, or both the members together express a

C₁-C₅ alkylidene group, or express a C₃-C₆ cyclic alkyl group in cooperation with the carbon atom to which they are bonded;

R₄₅ and R₄₆ are identical to or different from each other, and they express a hydrogen atom, a hydroxyl group, a trifluoromethyl group, a pentafluoroethyl group, a C₂-C₅ acyloxy group, a C₁-C₄ alkyloxy group or a C₁-C₄ alkyl group which may be substituted with a hydroxyl group, a C₂-C₅ acyloxy group or a C₁-C₄ alkyloxy group;

D and E express each a hydrogen atom, D is a hydroxy group and E expresses a hydrogen atom, D and E together express a single bond and express a double bond in cooperation with the single bond already shown in the formula, or E and R₄₁ together express a single bond and express a double bond in cooperation with the single bond already shown in the formula, wherein D expresses a hydrogen atom or a hydroxy group; and R₄₂ expresses a hydrogen atom, a hydroxyl group, a trifluoromethyl group, a pentafluoroethyl group, a C₂-C₅ acyloxy group, a C₁-C₄ alkyloxy group or a C₁-C₄ alkyl group which may be substituted with a hydroxyl group, a C₂-C₅ acyloxy group or a C₁-C₄ alkyloxy group;

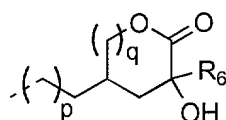
R₅₁ expresses -CONR₅₁₁R₅₁₂, -COR₅₁₃ or -C(OH)R₅₁₄R₅₁₅, wherein R₅₁₁ and R₅₁₂ are identical to or different from each other, and they are a hydrogen atom or a C₁-C₄ alkyl group, or both the members together express a nitrogen-containing C₃-C₈ alkyl ring or a morpholino group in cooperation with the nitrogen atom to which they are bonded; and R₅₁₃, R₅₁₄ and R₅₁₅ are identical to or different from each other, and they express a C₁-C₄ alkyl group;

R₅₂ expresses a methyl group, an ethyl group, a trifluoromethyl group or a pentafluoroethyl group,]

with the proviso that the following compounds (a), (b) and (c) are excluded,

(a) a compound in which the groups of one combination out of R_{21} and R_{22} , R_{32} and R_{33} , R_{34} and R_{35} , R_{41} and R_{42} , R_{43} and R_{44} , and R_{45} and R_{46} are both hydroxy groups, both alkyloxy groups, or a hydroxy group and an alkyloxy group,

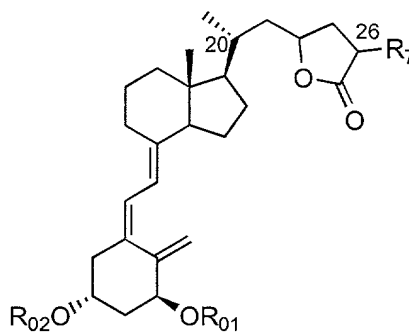
(b) a compound expressed by the above formula (1) in which Z is the following formula (1-6),



(1-6)

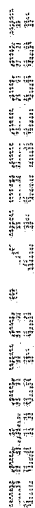
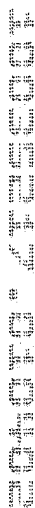
(wherein, p and q are each 0 or the integer 1; R₆ is a hydrogen atom or a C₁-C₄ alkyl group), and

(c) a compound of the following formula (2),



(2)

(wherein, R₀₁ and R₀₂ are defined in the same manner as in the above formula (1); the configuration of the carbon atom at the 20-position is (R)-configuration; R₇ is a methyl group or a methylene group; when R₇ is a methylene group, the bond between R₇ and the carbon atom at the 26-position is double bond)).

[illegible][illegible][illegible][illegible][illegible][illegible][illegible]

R₂₁, R₂₂ and R₂₃ are identical to or different from each other, and they are a hydrogen atom, a hydroxy group, a carboxyl group, a trifluoromethyl group, a pentafluoroethyl group, a C₁-C₄ alkyloxycarbonyl group, a C₂-C₅ acyloxy group, a C₁-C₄ alkyloxy group or a C₁-C₄ alkyl group which may be substituted with a hydroxyl group, a C₂-C₅ acyloxy group or a C₁-C₄ alkyloxy group, or R₂₁ and R₂₂ together may express a C₃-C₆ cyclic alkyl group in cooperation with the carbon atom to which they are bonded;

Q expresses >C(-F)-R₃₁ or >N-R₃₁, and herein R₃₁ is a hydrogen atom, a hydroxyl group, a trifluoromethyl group, a pentafluoroethyl group, a C₂-C₅ acyloxy group, a C₁-C₄ alkyloxy group or a C₁-C₄ alkyl group which may be substituted with a hydroxy group, a C₂-C₅ acyloxy group or a C₁-C₄ alkyloxy group;

R₃₂, R₃₃, R₃₄ and R₃₅ are identical to or different from each other, and they are a hydrogen atom, a hydroxyl group, a C₁-C₄ alkyl group or a C₂-C₅ acyloxy group;

A and B are identical to or different from each other, and they express a hydrogen atom or a hydroxyl group, or together express a single bond and form a double bond in cooperation with the single bond already shown in the formula;

X and Y together express a carbonyl group in cooperation with the carbon atom to which they are bonded, one of them is a hydrogen atom and the other is a hydroxyl group, or one of them is a hydrogen atom and the other is a C₂-C₅ acyloxy group;

R₄₁ and R₄₂ are identical to or different from each other, and they express a hydrogen atom, a hydroxyl group, a trifluoromethyl group, a pentafluoroethyl group, a C₂-C₅ acyloxy group, a C₁-C₄ alkyloxy group or a C₁-C₄ alkyl group which may be substituted with a hydroxyl group, a C₂-C₅ acyloxy group or a C₁-C₄ alkyloxy group, or both the members together express a

C₁-C₅ alkylidene group, or they express a C₃-C₆ cyclic alkyl group in cooperation with the carbon atom to which they are bonded;

R₄₃ and R₄₄ are identical to or different from each other, and they express a hydrogen atom, a hydroxyl group, a trifluoromethyl group, a pentafluoroethyl group, a C₂-C₅ acyloxy group, a C₁-C₄ alkyloxy group or a C₁-C₄ alkyl group which may be substituted with a hydroxyl group, a C₂-C₅ acyloxy group or a C₁-C₄ alkyloxy group, or both the members together express a C₁-C₅ alkylidene group, or express a C₃-C₆ cyclic alkyl group in cooperation with the carbon atom to which they are bonded;

R₄₅ and R₄₆ are identical to or different from each other, and they express a hydrogen atom, a hydroxyl group, a trifluoromethyl group, a pentafluoroethyl group, a C₂-C₅ acyloxy group, a C₁-C₄ alkyloxy group or a C₁-C₄ alkyl group which may be substituted with a hydroxyl group, a C₂-C₅ acyloxy group or a C₁-C₄ alkyloxy group;

D and E express each a hydrogen atom, D is a hydroxy group and E expresses a hydrogen atom, D and E together express a single bond and express a double bond in cooperation with the single bond already shown in the formula, or E and R₄₁ together express a single bond and express a double bond in cooperation with the single bond already shown in the formula, wherein D expresses a hydrogen atom or a hydroxy group; and R₄₂ expresses a hydrogen atom, a hydroxyl group, a trifluoromethyl group, a pentafluoroethyl group, a C₂-C₅ acyloxy group, a C₁-C₄ alkyloxy group or a C₁-C₄ alkyl group which may be substituted with a hydroxyl group, a C₂-C₅ acyloxy group or a C₁-C₄ alkyloxy group;

R₅₁ expresses -CONR₅₁₁R₅₁₂, -COR₅₁₃ or -C(OH) R₅₁₄R₅₁₅, wherein R₅₁₁ and R₅₁₂ are identical to or different from each other, and they are a hydrogen atom or a C₁-C₄ alkyl group, or

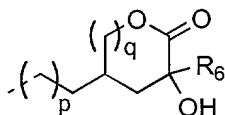
both the members together express a nitrogen-containing C₃-C₈ alkyl ring or a morpholino group in cooperation with the nitrogen atom to which they are bonded; and R₅₁₃, R₅₁₄ and R₅₁₅ are identical to or different from each other, and they express a C₁-C₄ alkyl group;

R₅₂ expresses a methyl group, an ethyl group, a trifluoromethyl group or a pentafluoroethyl group,]

with the proviso that the following compounds (a), (b) and (c) are excluded,

(a) a compound in which the groups of one combination out of R₂₁ and R₂₂, R₃₂ and R₃₃, R₃₄ and R₃₅, R₄₁ and R₄₂, R₄₃ and R₄₄, and R₄₅ and R₄₆ are both hydroxy groups, both alkyloxy groups, or a hydroxy group and an alkyloxy group,

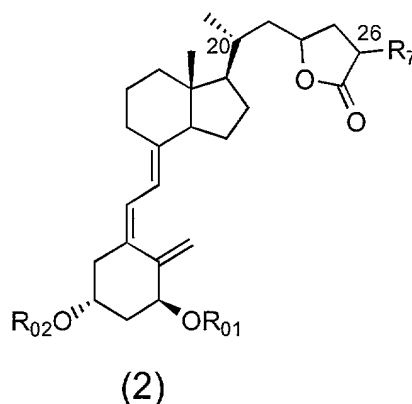
(b) a compound expressed by the above formula (1) in which Z is the following formula (1-6),



(1-6)

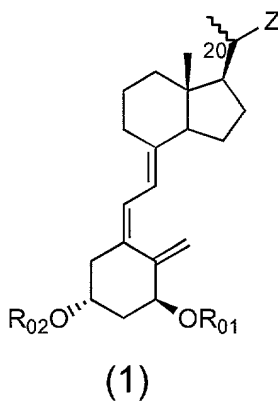
(wherein, p and q are each 0 or the integer 1; R₆ is a hydrogen atom or a C₁-C₄ alkyl group), and

(c) a compound of the following formula (2),



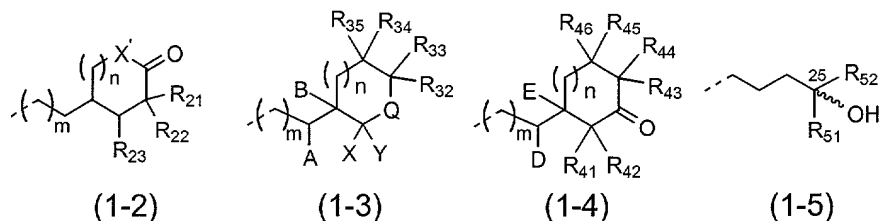
(wherein, R_{01} and R_{02} are defined in the same manner as in the above formula (1); the configuration of the carbon atom at the 20-position is (R)-configuration; R_7 is a methyl group or a methylene group; when R_7 is a methylene group, the bond between R_7 and the carbon atom at the 26-position is double bond)).

53. A method for treating hypoparathyroidism comprising administering to a subject a therapeutically effective amount of a vitamin D_3 derivative of the following Formula (1) or pharmaceutically permissible solvate thereof,



{wherein, R_{01} and R_{02} are each independently a hydrogen atom, a trimethylsilyl group, a triethylsilyl group, a t-butyltrimethylsilyl group, an acetyl group, a methoxymethyl group or a tetrahydro-4H-pyran-2-yl group;

Z is one out of the following formulae (1-2), (1-3), (1-4) or (1-5),



[in the above formulae (1-2) to (1-5),

m is an integer of 0 to 2;

n is an integer of 0 to 2;

X' is an oxygen atom or NH;

R₂₁, R₂₂ and R₂₃ are identical to or different from each other, and they are a hydrogen atom, a hydroxy group, a carboxyl group, a trifluoromethyl group, a pentafluoroethyl group, a C₁-C₄ alkyloxycarbonyl group, a C₂-C₅ acyloxy group, a C₁-C₄ alkyloxy group or a C₁-C₄ alkyl group which may be substituted with a hydroxyl group, a C₂-C₅ acyloxy group or a C₁-C₄ alkyloxy group, or R₂₁ and R₂₂ together may express a C₃-C₆ cyclic alkyl group in cooperation with the carbon atom to which they are bonded;

Q expresses >C(-F)-R₃₁ or >N-R₃₁, and herein R₃₁ is a hydrogen atom, a hydroxyl group, a trifluoromethyl group, a pentafluoroethyl group, a C₂-C₅ acyloxy group, a C₁-C₄ alkyloxy group or a C₁-C₄ alkyl group which may be substituted with a hydroxy group, a C₂-C₅ acyloxy group or a C₁-C₄ alkyloxy group;

R₃₂, R₃₃, R₃₄ and R₃₅ are identical to or different from each other, and they are a hydrogen atom, a hydroxyl group, a C₁-C₄ alkyl group or a C₂-C₅ acyloxy group;

A and B are identical to or different from each other, and they express a hydrogen atom or a hydroxyl group, or together express a single bond and form a double bond in cooperation with the single bond already shown in the formula;

X and Y together express a carbonyl group in cooperation with the carbon atom to which they are bonded, one of them is a hydrogen atom and the other is a hydroxyl group, or one of them is a hydrogen atom and the other is a C₂-C₅ acyloxy group;

R₄₁ and R₄₂ are identical to or different from each other, and they express a hydrogen atom, a hydroxyl group, a trifluoromethyl group, a pentafluoroethyl group, a C₂-C₅ acyloxy group, a C₁-C₄ alkyloxy group or a C₁-C₄ alkyl group which may be substituted with a hydroxyl group, a C₂-C₅ acyloxy group or a C₁-C₄ alkyloxy group, or both the members together express a C₁-C₅ alkylidene group, or they express a C₃-C₆ cyclic alkyl group in cooperation with the carbon atom to which they are bonded;

R₄₃ and R₄₄ are identical to or different from each other, and they express a hydrogen atom, a hydroxyl group, a trifluoromethyl group, a pentafluoroethyl group, a C₂-C₅ acyloxy group, a C₁-C₄ alkyloxy group or a C₁-C₄ alkyl group which may be substituted with a hydroxyl group, a C₂-C₅ acyloxy group or a C₁-C₄ alkyloxy group, or both the members together express a C₁-C₅ alkylidene group, or express a C₃-C₆ cyclic alkyl group in cooperation with the carbon atom to which they are bonded;

R₄₅ and R₄₆ are identical to or different from each other, and they express a hydrogen atom, a hydroxyl group, a trifluoromethyl group, a pentafluoroethyl group, a C₂-C₅ acyloxy group, a C₁-C₄ alkyloxy group or a C₁-C₄ alkyl group which may be substituted with a hydroxyl group, a C₂-C₅ acyloxy group or a C₁-C₄ alkyloxy group;

D and E express each a hydrogen atom, D is a hydroxy group and E expresses a hydrogen atom, D and E together express a single bond and express a double bond in cooperation with the single bond already shown in the formula, or E and R₄₁ together express a single bond and express a double bond in cooperation with the single bond already shown in the formula, wherein D expresses a hydrogen atom or a hydroxy group; and R₄₂ expresses a hydrogen atom, a hydroxyl group, a trifluoromethyl group, a pentafluoroethyl group, a C₂-C₅ acyloxy group, a C₁-C₄ alkyloxy group or a C₁-C₄ alkyl group which may be substituted with a hydroxyl group, a C₂-C₅ acyloxy group or a C₁-C₄ alkyloxy group;

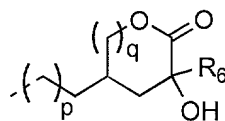
R₅₁ expresses -CONR₅₁₁R₅₁₂, -COR₅₁₃ or -C(OH) R₅₁₄R₅₁₅, wherein R₅₁₁ and R₅₁₂ are identical to or different from each other, and they are a hydrogen atom or a C₁-C₄ alkyl group, or both the members together express a nitrogen-containing C₃-C₈ alkyl ring or a morpholino group in cooperation with the nitrogen atom to which they are bonded; and R₅₁₃, R₅₁₄ and R₅₁₅ are identical to or different from each other, and they express a C₁-C₄ alkyl group;

R₅₂ expresses a methyl group, an ethyl group, a trifluoromethyl group or a pentafluoroethyl group,]

with the proviso that the following compounds (a), (b) and (c) are excluded,

(a) a compound in which the groups of one combination out of R₂₁ and R₂₂, R₃₂ and R₃₃, R₃₄ and R₃₅, R₄₁ and R₄₂, R₄₃ and R₄₄, and R₄₅ and R₄₆ are both hydroxy groups, both alkyloxy groups, or a hydroxy group and an alkyloxy group,

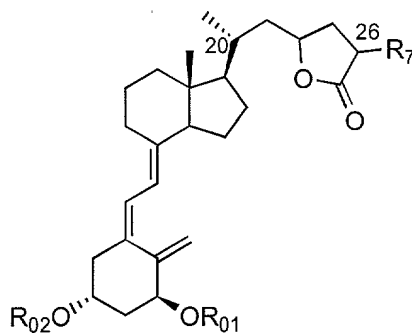
(b) a compound expressed by the above formula (1) in which Z is the following formula (1-6),



(1-6)

(wherein, p and q are each 0 or the integer 1; R_6 is a hydrogen atom or a C_1 - C_4 alkyl group), and

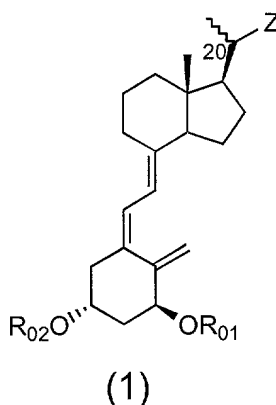
(c) a compound of the following formula (2),



(2)

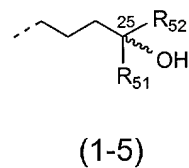
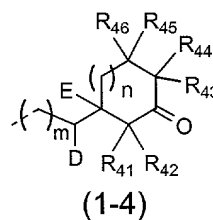
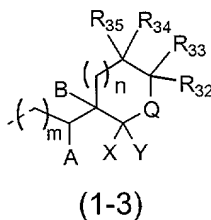
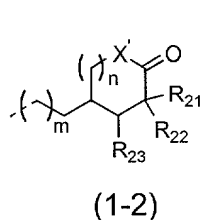
(wherein, R_{01} and R_{02} are defined in the same manner as in the above formula (1); the configuration of the carbon atom at the 20-position is (R)-configuration; R_7 is a methyl group or a methylene group; when R_7 is a methylene group, the bond between R_7 and the carbon atom at the 26-position is double bond)).

54. A method for treating metabolic disorder of cartilage comprising administering to a subject a therapeutically effective amount of a vitamin D_3 derivative of the following Formula (1) or pharmaceutically permissible solvate thereof,



{wherein, R_{01} and R_{02} are each independently a hydrogen atom, a trimethylsilyl group, a triethylsilyl group, a t-butyldimethylsilyl group, an acetyl group, a methoxymethyl group or a tetrahydro-4H-pyran-2-yl group;

Z is one out of the following formulae (1-2), (1-3), (1-4) or (1-5),



[in the above formulae (1-2) to (1-5),

m is an integer of 0 to 2;

n is an integer of 0 to 2;

X' is an oxygen atom or NH;

R_{21} , R_{22} and R_{23} are identical to or different from each other, and they are a hydrogen atom, a hydroxy group, a carboxyl group, a trifluoromethyl group, a pentafluoroethyl group, a C_1 - C_4 alkyloxycarbonyl group, a C_2 - C_5 acyloxy group, a C_1 - C_4 alkyloxy group or a C_1 - C_4 alkyl group which may be substituted with a hydroxyl group, a C_2 - C_5 acyloxy group or a C_1 - C_4

alkyloxy group, or R_{21} and R_{22} together may express a C_3 - C_6 cyclic alkyl group in cooperation with the carbon atom to which they are bonded;

Q expresses $>C(-F)-R_{31}$ or $>N-R_{31}$, and herein R_{31} is a hydrogen atom, a hydroxyl group, a trifluoromethyl group, a pentafluoroethyl group, a C_2 - C_5 acyloxy group, a C_1 - C_4 alkyloxy group or a C_1 - C_4 alkyl group which may be substituted with a hydroxy group, a C_2 - C_5 acyloxy group or a C_1 - C_4 alkyloxy group;

R_{32} , R_{33} , R_{34} and R_{35} are identical to or different from each other, and they are a hydrogen atom, a hydroxyl group, a C_1 - C_4 alkyl group or a C_2 - C_5 acyloxy group;

A and B are identical to or different from each other, and they express a hydrogen atom or a hydroxyl group, or together express a single bond and form a double bond in cooperation with the single bond already shown in the formula;

X and Y together express a carbonyl group in cooperation with the carbon atom to which they are bonded, one of them is a hydrogen atom and the other is a hydroxyl group, or one of them is a hydrogen atom and the other is a C_2 - C_5 acyloxy group;

R_{41} and R_{42} are identical to or different from each other, and they express a hydrogen atom, a hydroxyl group, a trifluoromethyl group, a pentafluoroethyl group, a C_2 - C_5 acyloxy group, a C_1 - C_4 alkyloxy group or a C_1 - C_4 alkyl group which may be substituted with a hydroxyl group, a C_2 - C_5 acyloxy group or a C_1 - C_4 alkyloxy group, or both the members together express a C_1 - C_5 alkylidene group, or they express a C_3 - C_6 cyclic alkyl group in cooperation with the carbon atom to which they are bonded;

R_{43} and R_{44} are identical to or different from each other, and they express a hydrogen atom, a hydroxyl group, a trifluoromethyl group, a pentafluoroethyl group, a C_2 - C_5 acyloxy

group, a C₁-C₄ alkyloxy group or a C₁-C₄ alkyl group which may be substituted with a hydroxyl group, a C₂-C₅ acyloxy group or a C₁-C₄ alkyloxy group, or both the members together express a C₁-C₅ alkylidene group, or express a C₃-C₆ cyclic alkyl group in cooperation with the carbon atom to which they are bonded;

R₄₅ and R₄₆ are identical to or different from each other, and they express a hydrogen atom, a hydroxyl group, a trifluoromethyl group, a pentafluoroethyl group, a C₂-C₅ acyloxy group, a C₁-C₄ alkyloxy group or a C₁-C₄ alkyl group which may be substituted with a hydroxyl group, a C₂-C₅ acyloxy group or a C₁-C₄ alkyloxy group;

D and E express each a hydrogen atom, D is a hydroxy group and E expresses a hydrogen atom, D and E together express a single bond and express a double bond in cooperation with the single bond already shown in the formula, or E and R₄₁ together express a single bond and express a double bond in cooperation with the single bond already shown in the formula, wherein D expresses a hydrogen atom or a hydroxy group; and R₄₂ expresses a hydrogen atom, a hydroxyl group, a trifluoromethyl group, a pentafluoroethyl group, a C₂-C₅ acyloxy group, a C₁-C₄ alkyloxy group or a C₁-C₄ alkyl group which may be substituted with a hydroxyl group, a C₂-C₅ acyloxy group or a C₁-C₄ alkyloxy group;

R₅₁ expresses -CONR₅₁₁R₅₁₂, -COR₅₁₃ or -C(OH) R₅₁₄R₅₁₅, wherein R₅₁₁ and R₅₁₂ are identical to or different from each other, and they are a hydrogen atom or a C₁-C₄ alkyl group, or both the members together express a nitrogen-containing C₃-C₈ alkyl ring or a morpholino group in cooperation with the nitrogen atom to which they are bonded; and R₅₁₃, R₅₁₄ and R₅₁₅ are identical to or different from each other, and they express a C₁-C₄ alkyl group;

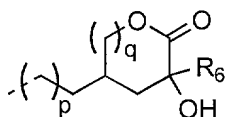
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R₅₂ expresses a methyl group, an ethyl group, a trifluoromethyl group or a pentafluoroethyl group,]

with the proviso that the following compounds (a), (b) and (c) are excluded,

(a) a compound in which the groups of one combination out of R₂₁ and R₂₂, R₃₂ and R₃₃, R₃₄ and R₃₅, R₄₁ and R₄₂, R₄₃ and R₄₄, and R₄₅ and R₄₆ are both hydroxy groups, both alkyloxy groups, or a hydroxy group and an alkyloxy group,

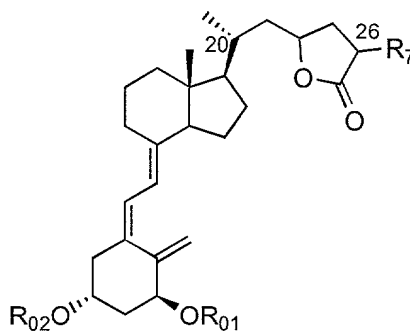
(b) a compound expressed by the above formula (1) in which Z is the following formula (1-6),



(1-6)

(wherein, p and q are each 0 or the integer 1; R₆ is a hydrogen atom or a C₁-C₄ alkyl group), and

(c) a compound of the following formula (2),



(2)

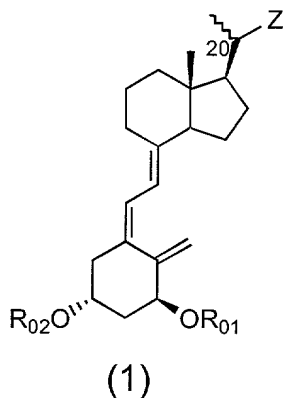
(wherein, R₀₁ and R₀₂ are defined in the same manner as in the above formula (1); the configuration of the carbon atom at the 20-position is (R)-configuration; R₇ is a methyl group or

a methylene group; when R₇ is a methylene group, the bond between R₇ and the carbon atom at the 26-position is double bond)).

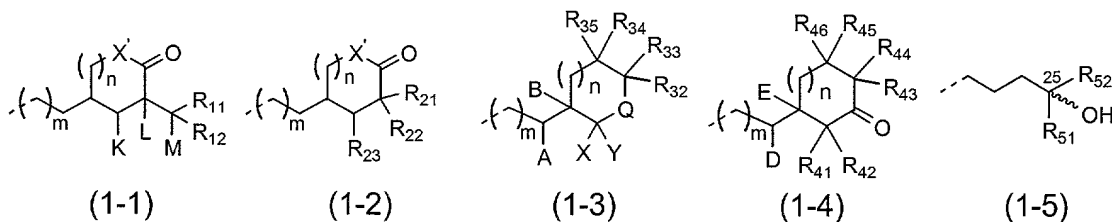
IN THE ABSTRACT OF DISCLOSURE:

Please delete the present Abstract of the Disclosure and replace it with the following new Abstract of the Disclosure:

Compounds expressed by the following general formula (1),



[wherein, R₀₁ and R₀₂ are each independently a hydrogen atom or a protecting group for a hydroxyl group; Z is one out of the following formulae (1-1), (1-2), (1-3), (1-4) and (1-5)].



The compounds can be used as active ingredients of treating agents for inflammatory respiratory diseases, malignant tumors, rheumatoid arthritis, osteoporosis, diabetes mellitus, hypertension,

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alopecia, acne, psoriasis, dermatitis, hypercalcemia, hypoparathyroidism and metabolic disorder
of cartilage.

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REMARKS

The specification and the Abstract have been amended to correct an inadvertent error in formulae (1-1) and (1-2) for Z, wherein X in the formulae has been changed to X'. The basis for the change can be seen in the subsequent disclosure of X' at, e.g., page 7, line 1, and the overall disclosure at, e.g., page 6, line 18 to page 7, line 9 in the application.

New claims 45-54 merely convert original claims 33 and 35-43 to method claims.

New claims 45-54 correspond to the Group VII claims in the Restriction Requirement issued October 4, 2001 in parent application 09/830,167.

Entry of the above amendment is respectfully requested.

Respectfully submitted,



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Date: *January 4, 2002*

APPENDIX

VERSION WITH MARKINGS TO SHOW CHANGES MADE

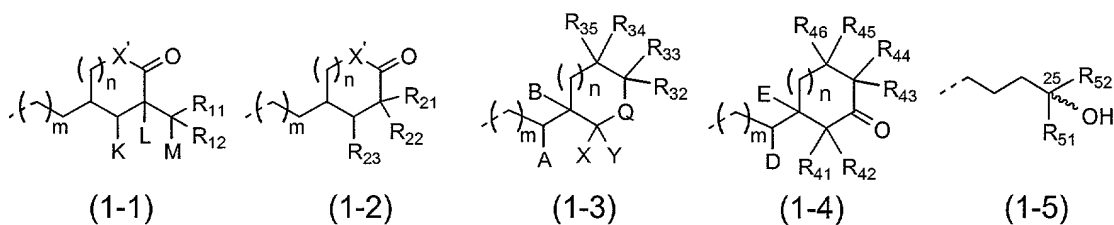
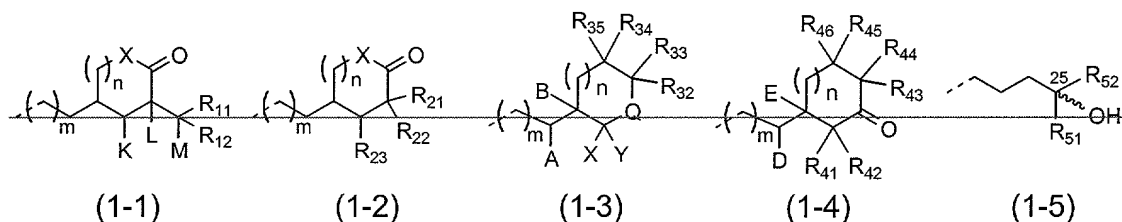
IN THE SPECIFICATION:

Amend the specification by inserting before the first line of the sentence:

This is a Divisional of Application No. 09/830,167 filed April 23, 2001, the disclosure

of which is incorporated herein by reference.

Page 6, the paragraph at lines 18-19 with formulas (1-1) to (1-5):



IN THE CLAIMS:

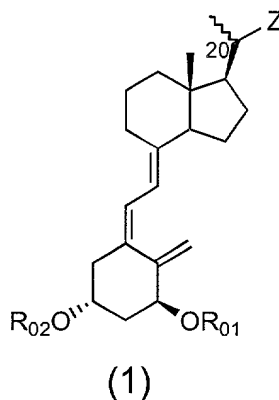
Claims 1-44 are canceled.

Claims 45-54 are added.

IN THE ABSTRACT OF DISCLOSURE:

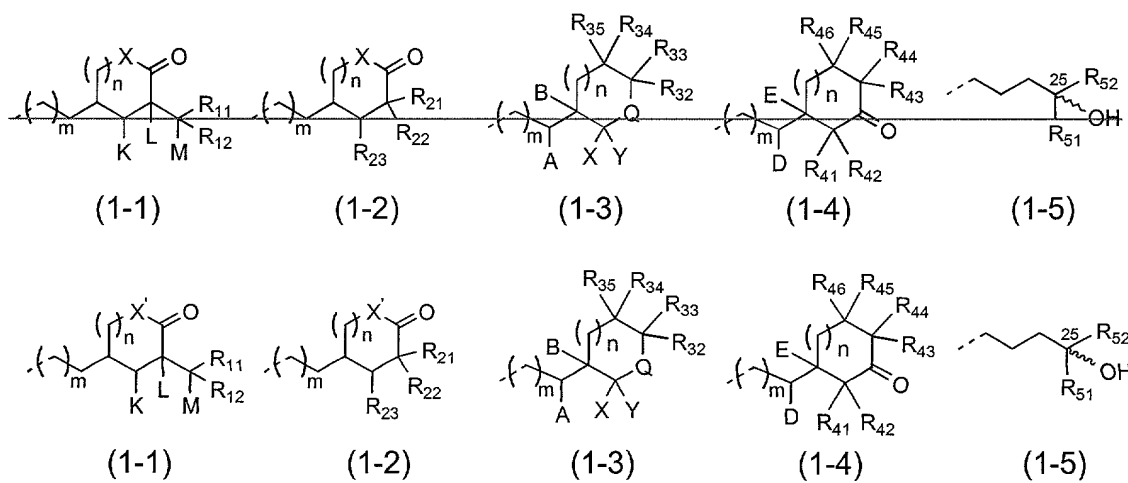
The abstract is changed as follows:

Compounds expressed by the following general formula (1),



[wherein, R_{01} and R_{02} are each independently a hydrogen atom or a protecting group for a

hydroxyl group; Z is one out of the following formulae (1-1), (1-2), (1-3), (1-4) and (1-5)].



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The compounds can be used as active ingredients of treating agents for inflammatory respiratory diseases, malignant tumors, rheumatoid arthritis, osteoporosis, diabetes mellitus, hypertension, alopecia, acne, psoriasis, dermatitis, hypercalcemia, hypoparathyroidism and metabolic disorder of cartilage.